Journal of Surgical Oncology 61:27–33 (1996)

Medullary Thyroid Carcinoma Experienced at Kanazawa University Hospital

YUJI MIZUKAMI, MD, AKITAKA NONOMURA, MD, TAKATOSHI MICHIGISHI, MD, MASAKUNI NOGUCHI, MD, SHINOBU OHTAKE, MD, SHINOBU NAKAMURA, MD, AND TAKESHI ISHIZAKI, MD

From the Pathology Section (Y.,M., A.N.) and the Departments of Nuclear Medicine (T.M.), Surgery (M.N.), and Internal Medicine (S.O., S.N.), Kanazawa University Hospital, Kanazawa, Japan; and the Department of Internal Medicine (T.I.), Fukui Medical School, Fukui, Japan

Eleven cases of medullary thyroid carcinoma (MTC), which were experienced at Kanazawa University Hospital between 1975 and 1993, were examined to correlate the clinical, histologic, and immunohistochemical findings. Seven patients were women and four men, and the mean age was 46.6 years. The mean follow-up was 88.3 months. Three patients had familial non-multiple endocrine neoplasia (MEN) MTC (familial MTC unassociated with other endocrinopathies) and the remaining eight had sporadic disease. At the end of the observation period, six patients were alive without disease and four were alive with metastatic disease. One patient died of MTC 8.3 years after surgery. Thus, the 10-year survival and disease-free survival rates were 67% and 53%, respectively. Histologically MTCs from the 10 surviving patients showed a classic type, while the one patient who died had a tubular variant MTC. Immunohistochemically, there were no significant correlations between the outcome of the patients and the expression of calcitonin (CT), carcinoembryonic antigen (CEA), calcitonin gene-related peptide (CGRP), or chromogranin A (CgA) in the primary tumors, and there were no differences in expression of these antigens between the primary and the recurrent tumors.

Although only a small number of patients with MTC were studied here, it was suggested that the prognosis of MTC is worse than that of papillary and follicular thyroid carcinoma. The patients with lymph node involvement at the time of primary surgery showed a high risk of persistent or recurrent disease. The expressional level for the antigens did not influence the prognosis of MTC. © 1996 Wiley-Liss, Inc.

KEY WORDS: **medullary thyroid carcinoma, histology, immunohistochemistry, prognosis**

INTRODUCTION

Medullary thyroid carcinoma (MTC), which accounts for 5–10% of all thyroid cancers in the United States and other Western countries [1,2] and 1–2% in Japan [3,4], arises from calcitonin (CT)-producing parafollicular (C-) cells of the thyroid. This thyroid tumor occurs in a sporadic and a famililar form. This tumor is also characterized by the ability to produce several hormonal and nonhormonal substances, such as CT, carcinoembryonic antigen (CEA), calcitonin gene-related peptide (CGRP), chromogranin A (CgA), neuron-specific enolase, and somatostatin [1,2].

MTC has a natural history that may vary from indolent

Accepted for publication September 12, 1995.

Address reprint requests to Dr. Yuji Mizukami, Pathology Section, Kanazawa University Hospital, 13-1, Takara-machi, Kanazawa, 920, Japan.

© 1996 Wiley-Liss, Inc.

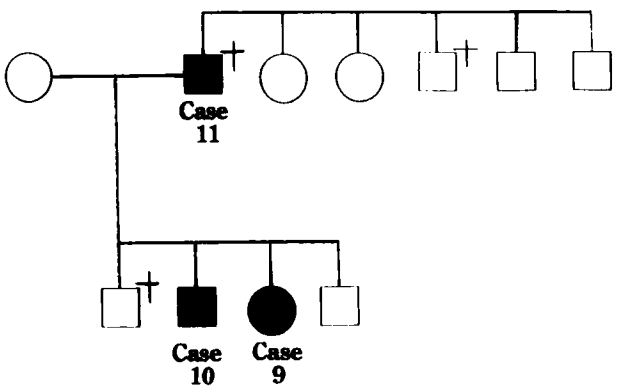

Fig. 1. Pedigree of a family with familial non-MEN MTC (Cases 9, 10, and 11). □, male; ○, female; •, MTC; †, died

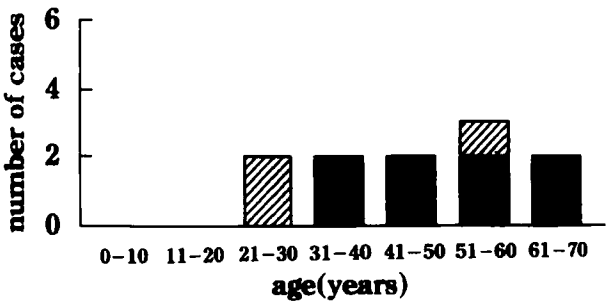

Fig. 2. Age distribution of 11 patients with MTC at initial surgery. Familial (hatched bars) and sporadic (full columns) forms.

to aggressive, but in general its prognosis is worse than that of papillary and follicular thyroid carcinoma [5–9]. To date, many factors, such as tumor stage, inheritance pattern, histologic features, DNA ploidy status, and capacity to produce CT and other hormonal and nonhormonal products, have been proved to be valuable in predicting outcome [5–14].

In the present study, we retrospectively analyzed our personal experience with 11 patients with MTC during the past 19 years in our hospital. The clinical, histologic, and immunohistochemical results were correlated with the patients' outcome.

PATIENTS AND METHODS

Patients

Eleven cases diagnosed with MTC from the files of the surgical pathology section of Kanazawa University Hospital (Kanazawa) between 1975 to 1993 were included in this study. There were eight cases with sporadic MTC and three with familial non-multiple endocrine neoplasia (MEN) MTC (familial MTC unassociated with other endocrinopathies) which occurred in one family (Fig. 1). Seven patients were women and four men, and the mean age for the group was 46.6 years (range 25–64 years) (Fig. 2). Mean overall follow-up was 88.3 months (20–231 months; Table I).

Regional lymph node metastases were present in seven patients and absent in the remaining four at diagnosis. Eight patients were treated initially by total thyroidectomy and the remaining three by subtotal thyroidectomy. One patient underwent a radical neck dissection, seven modified radical neck dissection, and three simple neck dissection. Four patients required one or more reoperations during the follow-up period for recurrence of the disease.

Histologic Examination

Primary thyroid tumors and, if present, metastatic or local recurrent tumors were stained routinely with hematoxylin-eosin. Congo red staining for identification of amyloid and Grimelius silver staining were also performed in parallel. The histologic diagnosis and subclassification of MTC were done according to the WHO's and AFIP's histologic classification of thyroid tumors [15,16].

Immunohistochemical Examination

Immunohistochemical staining was performed using the avidin-biotin-peroxidase complex (ABC) method on formalin-fixed, paraffin-embedded tissue sections. The following antisera were used: polyclonal antibodies against thyroglobulin (TG; prediluted), CEA (1:200 dilution), CgA (1:200) (all Dako, Glostrup, Denmark), CT (1:2,000) (Chemicon Inc., Temecula, CA), and CGRP (1:2,000; Peninsula Laboratories Inc., Belmont, CA), and monoclonal antibody to CEA (1:40; Dako). The primary antisera were incubated overnight at 4°C. As a negative control, the primary antisera were replaced with nonimmune serum.

In each case, both the distribution (percentage of positive cells) and the intensity of staining were assessed in a semiquantitative fashion. The following system was employed to score the distribution and intensity of positive cells: (0) = negative, negative staining; (1) = minimal, marginal staining; (2) = mild, weak staining of all cells or stronger staining of a subpopulation group; (3) = moderate to intense, strong staining of all cells or a major subpopulation of cells.

RESULTS

The clinical and pathologic features of the 11 patients with MTC are summarized in Table I. The immunohistochemical staining results in the primary and, if present, the recurrent tumors from the 11 patients are shown in Table II.

Size of the Primary Tumor

The primary tumors measured from 0.8 to 5.0 cm in diameter. A medullary microcarcinoma was incidentally found in a 60-year-old woman with a thyroid adenoma

TABLE I. Clinical and and Pathologic Features of 11 Patients With MTC*

Case no.	Age (year)	Sex	Type of disease	Tumor size (cm)	Histologic pattern	Lymph node metastases	Therapy	Follow-up period	Outcome
1.	40	F	Sp	1.5	C (spindle cell)	A	TT + BMRND	7 yr 10 mo	Alive and well
2.	63	F	SP	2.5	C (pseudopapillary)	A	TT + BMRND	3 yr 3 mo	Alive and well
3.	48	F	Sp	3.0	C (polygonal cell)	A	STT + RMRND	5 yr 9 mo	Alive and well
4.	55	M	Sp	2.0	C (polygonal cell)	P	TT + BMRND	3 yr 6 mo	Alive and well
5.	60	F	Sp	0.8	C (spindle cell)	A	STT + ND	9 yr 3 mo	Alive and well
6.	45	M	Sp	1.5	C (polygonal cell)	P	TT + BMRND	1 yr 8 mo	Alive and well
7.	33	F	Sp	3.5	C (polygonal cell)	P	TT + ND	19 yr 3 mo	Alive with disease Node metastases, 3 yr Lung metastases, 18 yr
8.	64	F	Sp	1.7	C (polygonal cell)	P	STT + ND	7 yr 9 mo	Alive with disease Node metastases, 1 yr Occult node metastases
9.	25	F	Fa	1.2	C (pseudopapillary)	P	TT + BMRND	7 yr 4 mo	Alive with disease Persistent disease Occult node metastases
10.	27	M	Fa	3.0	C (pseudopapillary)	P	TT + BMRND	7 yr	Alive with disease Persistent disease Occult node metastases
11.	53	M	Fa	5.0	Tubular	P	TT + RND	8 yr 4 mo	Died of disease Persistent disease Widespread organ metastases

*Type of disease: Sp, sporadic, Fa, familial; histologic pattern: C, classic; lymph node metastases: P, present, A, absent; therapy: TT, total thyroidectomy, STT, subtotal thyroidectomy, B(R)MRND, bilateral (right side) modified radical neck dissection, RND, radical neck dissection, ND, neck dissection.

TABLE II. Summary of Immunohistochemical Staining and Congo Red Staining Results in Primary and Recurrent Tumors of 11 Patients With MTC*

Case no.	CT		CEA(p)		CEA(m)		CGRP		CgA		Amyloid
	P	R	P	R	P	R	P	R	P	R	P
1.	2+		3+		2+		2+		2+		Minimal
2.	2+		2+		2+		1+		2+		Abundant
3.	3+		3+		2+		2+		3+		Minimal
4.	2+		2+		2+		2+		2+		Moderate
5.	2+		2+		2+		2+		2+		Minimal
6.	3+		3+		3+		2+		3+		Minimal
7.	2+	2+	3+	3+	3+	3+	3+	2+	3+	3+	Abundant
8.	2+	2+	3+	2+	3+	2+	2+	2+	2+	2+	Moderate
9.	2+	ne	2+	ne	3+	ne	1+	ne	2+	ne	Moderate
10.	2+	2+	3+	3+	2+	2+	1+	1+	2+	2+	Moderate
11.	2+	2+	2+	2+	2+	3+	2+	3+	2+	2+	Minimal

*CT, calcitonin; CEA(p or m), carcinoembryonic antigen (detected using polyclonal or monoclonal antibody); CGRP, calcitonin gene-related peptide; CgA, chromogranin A; P, primary tumor; R, recurrent tumor.

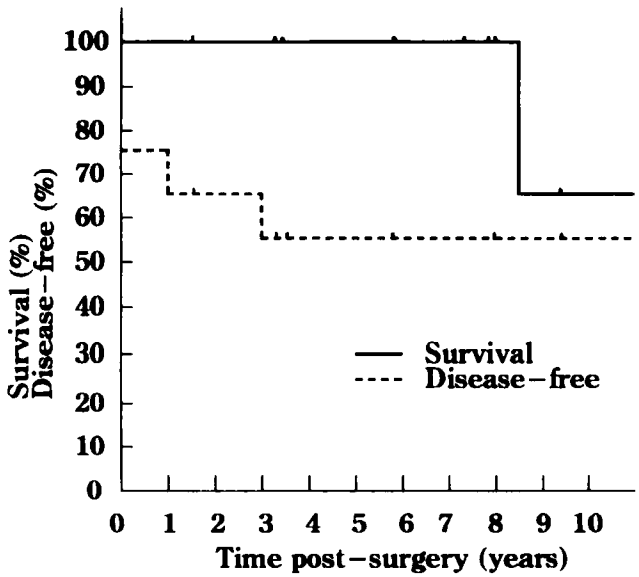

Fig. 3. Survival and disease-free survival curves in 11 patients with MTC (Kaplan-Meier method).

(Case 5) [17]. Of the three patients with familial MTC, the tumor involved nearly the entire thyroid gland in one patient (Case 11), while a single tumor in the thyroid gland was found in the remaining two patients (Cases 9 and 10).

Prognosis of Patients

The survival and disease-free survival curves of the 11 patients constructed using the Kaplan-Meier method are shown in Figure 3. The 10-year survival and disease-free survival rates were 67% and 53%, respectively. After initial operation, persistent (residual) disease (persistent elevated CT levels with or without clinically evident tumor) was present in three patients. Recurrence of the disease occurred in two patients; one patient (Case 7) had node metastases 3 years and lung metastases 18 years

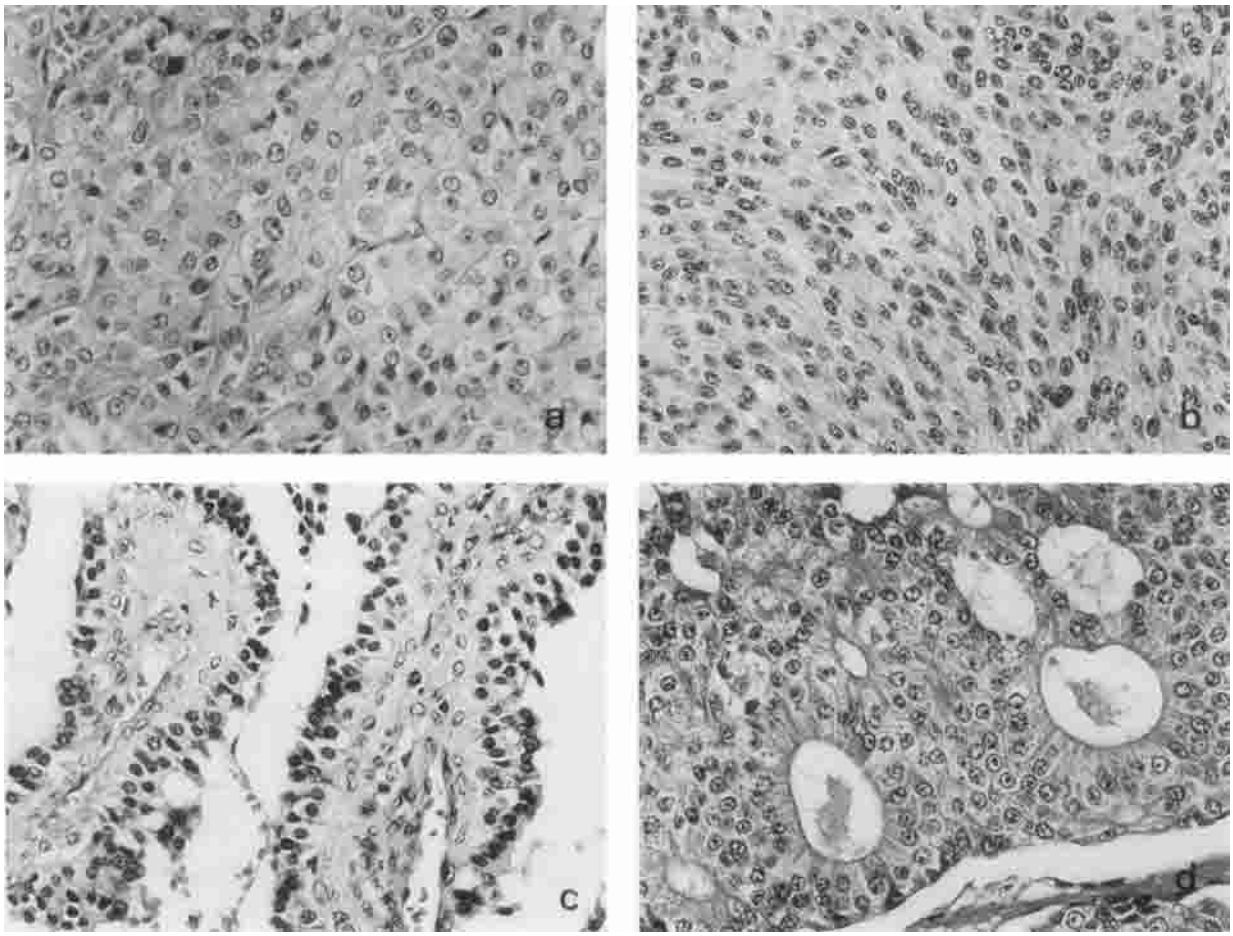

Fig. 4. Classic MTCs. **a:** Polygonal cell type. **b:** Spindle cell type. **c:** pseudopapillary growth type. **d:** Tubular variant of MTC. The tumor shows solid nests containing small tubules. (H&E, ×200).

after surgery and the other (Case 8) had node metastases 1 year after surgery. One patient (Case 11) died of disease 8.3 years after surgery. The autopsy examination showed widespread distant metastases of MTC to the lungs, liver, brain, and adrenals. At the end of the observation period, 10 patients were alive; 4 patients alive with disease and the remaining 6 alive with no evidence of disease.

Histologic Findings

The histologic subtypes of the 11 MTCs are shown in Table I. Classic (typical) MTC was found in 10 cases and the tubular variant of MTC in 1 (Fig. 4). Three cases of familial MTC which were found in one family were composed of tubular variant MTC in the father (Case 11) and classic MTCs (pseudopapillary pattern) in the two children (Cases 9 and 10). The tumors contained variable amounts of amyloid material from minimal to abundant. However, there was no correlation between the amount of amyloid materials in the tumors and the prognosis of the patients.

Immunohistochemical Findings

CT, CEA detectable using polyclonal or monoclonal antibody, CGRP, and CgA were detected in all cases (Table II). There were no correlations between the expression of these antigens in the primary tumors and the prognosis of the patients. The expressional levels of these antigens also did not differ between the primary and the recurrent tumors. In most cases, variable numbers of TG-positive cells or follicles were intermingled in the tumors, and in two cases (Cases 6 and 10) TG-positive follicles were present not only in the primary tumors but also in the node metastases, indicating that both cases had a mixed medullary-follicular carcinoma of the thyroid [18].

Serum Levels of CT and CEA

Preoperative and postoperative CT and CEA levels in the circulation were measured serially in the patients with persistent or recurrent disease. In three of the four patients examined, CT tended to be less intensely expressed as

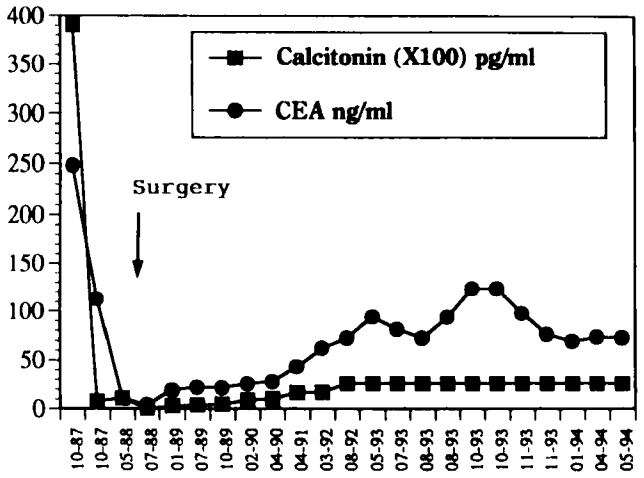

Fig. 5. Plasma concentrations of CT and CEA in a patient with MTC (Case 10), determined before, during, and after total thyroidectomy and neck dissection. Residual disease is shown by the persistently elevated levels of CT and CEA after surgery. Note an inversion in CT/CEA ratio at pre and postsurgery.

TABLE III. Histologic Distribution of Thyroid Cancers Experienced at Kanazawa University Hospital From 1975 to 1993

Histology	No. of cases (%)
Papillary carcinoma	667 (80.0)
Follicular carcinoma	87 (10.4)
Anaplastic carcinoma	5 (0.6)
Medullary carcinoma	11 (1.3)
Malignant lymphoma	10 (1.2)
Others	54 (6.5)
Total	834

the tumor progressed, while CEA tended to be more intensely expressed (Fig. 5). This finding in the circulation was not consistent with the immunohistochemical results, i.e., there were no differences in CT or CEA expression between the primary and the recurrent tumors in these cases.

DISCUSSION

We experienced a total of 11 cases of MTC in our hospital during the past 19 years. In the same period, we treated about 800 thyroid cancers in our hospital, and thus the frequency of MTC was 1.3% of all malignant tumors of the thyroid (Table III). Other studies in Japan have also described a similar frequency [3,4], whereas in the United States and other Western countries a much higher frequency has been found [1,2]. The reason why the frequency of MTC is low in Japan is not clear, but ethnic factors or the amount of dietary iodine intake might contribute to this difference [19,20].

There are two clinical types of MTC: a sporadic form which accounts for the majority of tumors (60–70%) and a less common familial (hereditary) form. At present, three variants are known in familial MTC: MEN type 2A, type 2B and familial MTC unassociated with other endocrinopathies (familial non-MEN MTC) [21]. It has been shown that the clinical behavior of MTC greatly varies in each clinical type; familial MTCs generally have a more favorable prognosis than the sporadic MTCs, and among familial MTCs familial non-MEN MTCs have the most favorable prognosis, followed by MEN 2A, and with MTCs occurring as a part of MEN 2B being the most aggressive form of the disease [22–27]. Farndon et al. [25] reported that none of 41 patients with familial non-MEN MTC died of MTC. In the present study, however, three patients with familial non-MEN MTC were found in one family, and one of the three patients died of disease while the remaining two had persistent disease. This suggested that the prognosis of familial non-MEN MTC is not necessarily as favorable as reported previously.

The clinical outcome of MTC might vary in individuals with the same clinical types (sporadic, MEN 2A, MEN 2B, or familial non-MEN MTC) or clinical stages. Therefore, many studies focused on the prediction of the prognosis of MTC have been reported, and histologic features, immunohistochemical staining pattern, and DNA ploidy pattern have been assessed as prognostic factors of MTC [5,6,8–14,26,28]. Classic (typical) MTCs consist of either nests or sheets of polygonal or spindle-shaped cells separated by variable amounts of amyloid and fibrous stroma. In addition to the classic MTCs, several histologic variants of MTCs have been reported including papillary [29], tubular (follicular) [29–31], oxyphilic [30,32], poorly differentiated [33], and anaplastic variants [34,35], some of which might influence the biologic behavior of MTC. The prognosis of the poorly differentiated or anaplastic type is known to be worse [33–35]. Sambade et al. [29] reported that the follicular variant of MTC is associated with a poorer prognosis in contrast to the papillary variant of MTC which carries a good prognosis. Oat cell and small cell variants have also been reported to carry a poor prognosis as compared to classic MTCs [36,37]. In the present study, although the one patient who died of MTC had a tubular variant of MTC, there were no differences in tumor histology between the patients surviving with disease and those without disease. Bergholm et al. [5] and Pyke et al. [38] reported that negative amyloid staining is a significant predictor of increased mortality rate. The present study, however, could not confirm this finding.

The immunostaining pattern of the products has also been claimed to be of prognostic value in MTC. CT content in MTC appears to be the best marker for tumor behavior; MTCs stained homogenously and intensely for CT have a better prognosis than CT-poor or heterogenously stained MTCs [8,10,12,14]. Saad et al. [8] reported a 5-year survival rate of 52% in patients with poor staining

for CT as compared with 100% in those with rich staining for CT. CEA also might be a reliable marker of follow-up in patients with MTC. In contrast to CT, staining intensity of CEA in metastatic foci was increasingly expressed as the tumor disseminated [8,10,12,14]. In the present study, we could not find a significant correlation between the staining intensity for CT and CEA in the primary tumors and the prognosis of the patients. In addition, the expressional levels of CT and CEA did not differ between the primary and the recurrent tumors. Our findings suggested that the immunostaining pattern of CT and CEA cannot become a prognostic indicator of MTC, as reported by Pacini et al. [13]. In the present study, more increased serum levels of CEA compared to CT were noted in accordance with tumor progression; however, a concomitant CEA over expression was not observed in the recurrent tumors. This discrepancy in CEA expression between the circulation and the tissues should be resolved in further studies.

In the present study, all five patients with persistent or recurrent disease had lymph node metastases at initial surgery. On the other hand, four patients with no node metastases at initial surgery were free from disease after surgery. It has been reported that 50–70% of palpable MTCs have already disseminated to the regional lymph nodes at the time of initial surgery and that once lymph node metastases occur, the prognosis of generally poor [6,26,38]. In contrast to papillary and follicular carcinoma, radioactive iodine is not effective for the metastases of MTC. Therefore, the authors propose that patients with MTC, either familial or sporadic, be treated by total thyroidectomy and complete dissection of lymph nodes.

In summary, we reviewed the clinical, histologic, and immunohistochemical findings of 11 cases of MTC. Although the number of cases examined in this series is small, it was found that MTC carries a worse prognosis than that of papillary and follicular thyroid carcinoma, the latter of which was defined in our previous prognostic study at our hospital [39]. Not only histologic, immunohistochemical, or DNA analysis, but also more recently developed oncogene or chromosome analysis should be included in the studies to clarify the pathobiology of MTC in the future [40].

ACKNOWLEDGMENTS

We thank Drs. Akira Sugenoya and Nobuo Itoh (School of Medicine, Shinshu University, Matsumoto), who kindly provided us with the clinical and pathologic data of the patients. We also thank Misses Yuki Makino and Hikari Note for their technical assistance.

REFERENCES

1. LiVolsi VA (ed): "Surgical Pathology of the Thyroid." Philadelphia: W.B. Saunders, 1990.
2. Ljungberg O (ed): "Biopsy Pathology of the Thyroid and Parathyroid." London: Chapman & Hall, 1992.
3. Ezaki H, Ebihara S, Fujimoto Y, et al.: Analysis of thyroid carcinoma based on material registered in Japan during 1977–1986 with special reference to predominance of papillary type. Cancer 70:808–814, 1992.
4. Koike A, Naruse T: Incidence of thyroid cancer in Japan. Semin Surg Oncol 7:107–111, 1991.
5. Bergholm U, Adami HO, Auer G, et al.: Histopathologic characteristics and nuclear DNA content as prognostic factors in medullary thyroid carcinoma. A nationwide study in Sweden. Cancer 64:135–142, 1989.
6. Hay ID, Ryan JJ, Grant CS, et al.: Prognostic significance of nondiploid DNA determination by flow cytometry in sporadic and familial medullary thyroid carcinoma. Surgery 108:972–980, 1990.
7. Kallinowski F, Buhr HJ, Meybier H, et al.: Medullary carcinoma of the thyroid—Therapeutic strategy derived from fifteen years of experience. Surgery 114:491–496, 1993.
8. Saad MF, Ordonez NG, Guido JJ, Samaan NA: The prognostic value of calcitonin immunostaining in medullary carcinoma of the thyroid. J Clin Endocrinol Metab 59:850–856, 1984.
9. Schroder S, Bocker W, Baisch H, et al.: Prognostic factors in medullary thyroid carcinomas: Survival in relation to age, sex, stage, histology, immunocytochemistry, and DNA content. Cancer 61:806–816, 1988.
10. El-Naggar AK, Ordonez NG, McLemore D, et al.: Clinicopathologic and flow cytometric DNA study of medullary thyroid carcinoma. Surgery 108:981–985, 1990.
11. Galera-Davidson H, Gonzalez-Campora R, Mora-Marin JA, et al: Cytophotometric DNA measurements in medullary thyroid carcinoma. Cancer 65:2255–2260, 1990.
12. Mendelsohn G, Wells SA, Baylin SB: Relationship of tissue carcinoembryonic antigen and calcitonin to tumor virulence in medullary thyroid carcinoma. An immunohistochemical study in early, localized, and virulent disseminated stages of disease. Cancer 54:657–662, 1984.
13. Pacini F, Basolo F, Elisei R, et al.: Medullary thyroid cancer. An immunohistochemical and humoral study using six separate antigens. Am J Clin Pathol 95:300–308, 1991.
14. Takami H, Bessho T, Kameya T, et al.: Immunohistochemical study of medullary thyroid carcinoma: Relationship of clinical features to prognostic factors in 36 patients. World J Surg 12:572–579, 1988.
15. Hedinger C, Williams ED, Sobin LH (eds): "International Histological Classification of Tumors, 2nd ed." Berlin: Springer-Verlag, 1988.
16. Rosai J, Carcangiu ML, DeLellis RA (eds): "Tumors of the Thyroid Gland. Atlas of Tumor Pathology, 3rd Series Fascicle 5." Washington, DC: Armed Forces Institute of Pathology, 1992.
17. Mizukami Y, Kurumaya H, Nonomura A, et al.: Sporadic medullary microcarcinoma of the thyroid. Histopathology 21:375–377, 1992.
18. Mizukami Y, Michigishi T, Nonomura A, et al.: Mixed medullary-follicular carcinoma of the thyroid occurring in familial form. Histopathology 22:284–287, 1993.
19. Goodman MT, Yoshizawa CN, Kolonel LN: Descriptive epidemiology of thyroid cancer in Hawaii. Cancer 62:1272–1281, 1988.
20. Spitz MR, Soder JG, Katz RL, et al.: Ethnic patterns of thyroid cancer incidence in the United States, 1973–1981. Int J Cancer 42:549–553, 1988.
21. Gagel RF, Robinson MF, Donovan DT, Alford BR: Medullary thyroid carcinoma: Recent progress. J Clin Endocrinol Metab 76:809–814, 1993.
22. de Bustros AC, Baylin SB: Medullary carcinoma of the thyroid. In Braverman LE, Utiger RD (eds): "The Thyroid, 6th ed." Philadelphia: Lippincott Co, 1991, p 1166–1183.
23. Decker RA: Long-term follow-up of a large North American kindred with multiple endocrine neoplasia type 2A. Surgery 112:1066–1073, 1992.
24. Duh QY, Sancho JJ, Greenspan FS, et al.: Medullary thyroid carcinoma: The need for early diagnosis and total thyroidectomy. Arch Surg 124:1206–1210, 1989.
25. Farndon JR, Leight GS, Dilley WG, et al.: Familial medullary thyroid carcinoma without associated endocrinopathies: A distinct clinical entity. Br j Surg 73:278–281, 1986.
26. Saad MF, Ordonez NG, Rashid RK, et al.: Medullary carcinoma of the thyroid: A study of the clinical features and prognostic factors in 161 patients. Medicine 63:319–342, 1984.

27. Vasen HFA, van der Feltz M, Raue F, et al.: The natural course of multiple endocrine neoplasia type IIb: A study of 18 cases. Arch Intern Med 152:1250–1252, 1992.
28. Harach HR, Bergholm U: Fatal sporadic medullary carcinoma of the thyroid. Endocrinol Pathol 4:53–59, 1993.
29. Sambade C, Baldaque-Faria A, Cardoso-Oliveira M, Sobrinho-Simoes M: Follicular and papillary variants of medullary carcinoma of the thyroid. Pathol Res Pract 184:98–103, 1989.
30. Harach HR, Bergholm U: Medullary (C cell) carcinoma of the thyroid with features of follicular oxyphilic cell tumors. Histopathology 13:645–656, 1988.
31. Lertprasertsuke N, Kakudo K, Nakamura A, et al.: C cell carcinoma of the thyroid: Follicular variant. Acta Pathol Jpn 39:393–399, 1989.
32. Dominguez-Malagon H, Delgado-Chavez R, Torres-Najera M, et al.: Oxyphil and squamous variants of medullary thyroid carcinoma. Cancer 63:1183–1188, 1989.
33. Kakudo K, Miyauchi A, Katayama S, Watanabe K: Ultrastructural study of poorly differentiated medullary carcinoma of the thyroid. Virchows Arch A Pathol Anat Histopathol 410:455–460, 1987.
34. Martinelli G, Bazzocchi F, Govoni E, Santini D: Anaplastic type of medullary thyroid carcinoma: an ultrastructural and immunohistochemical study. Virchows Arch [A] 400:61–67, 1983.
35. Mendelsohn G, Baylin SB, Bigner SH, et al.: Anaplastic variants of medullary thyroid carcinoma: A light-microscopic and immunohistochemical study. Am J Surg Pathol 4:333–341, 1980.
36. Eusebi V, Damiani SD, Riva C, et al.: Calcitonin free oat-cell carcinoma of the thyroid gland. Virchows Arch [A] 417:267–271, 1990.
37. Harach HR, Bergholm U: Small cell variant of medullary carcinoma of the thyroid with neuroblastoma-like features. Histopathology 21:378–380, 1992.
38. Pyke CM, Hay ID, Goellner JR, et al.: Prognostic significance of calcitonin immunoreactivity, amyloid staining, and flow cytometric DNA measurements in medullary thyroid carcinoma. Surgery 110:964–971, 1991.
39. Mizukami Y, Noguchi M, Michigishi T, et al.: Papillary thyroid carcinoma in Kanazawa, Japan: Prognostic significance of histological subtypes. Histopathology 20:243–250, 1992.
40. Mizukami Y, Michigishi T, Nonomura A, et al.: Thyroid carcinoma: Clinical, pathologic correlations. Crit Rev Oncol Hematol 18:67–102, 1995.